UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,224	08/19/2005	Hans-Konrad Mueller-Hermelink	043043-0358757	2578

27500 7590 07/31/2009

PILLSBURY WINTHROP SHAW PITTMAN LLP
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
07/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,224	MUELLER-HERMELINK ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-116,120-130,133 and 134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *133* is/are allowed.

6)☒ Claim(s) *111-116,120-130 and 134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed May 13, 2009 in response to the Office Action of December 22, 2008 is acknowledged and has been entered. Previously pending claims 117 to 119 and 135-154 have been cancelled. Claims 111-116, 120-130, 133 and 134 are currently being examined.

Declaration

2. The Declaration of Dr. Mueller-Hermelink and Dr. Vollmers under 37 CFR 1.132 filed May 13, 2009 is sufficient to overcome the rejection of claims 111-116, 120-130, 133 and 134 based upon by Brändlein et al. (Amer. Assoc. Can. Res., March 29, 2002, 43:970, abstract #4803, IDS) as set forth in the last Office action.

Rejections Maintained

Priority

4. The priority date for claims 111-116, 120-130, 133 and 134 remains or is July 2, 2003 and the priority date for claim 133 remains July 6, 2002 because Applicants state they do not concede the priority dates of the claims, but do not specifically present arguments, thus the priority dates are maintained for the reasons previously set forth. Additionally, given that the Declaration of Dr. Mueller-Hermelink and Dr. Vollmers under 37 CFR 1.132 filed May 13, 20 states that the PM-2 antibody or the hybridoma producing were not publicly available prior to July 2, 2003, thus claims depending on the deposited antibody or hybridoma are not supported prior to July 2, 2003.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 111-116 and 120-130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "wherein PM-2 antibody produced by a cell line deposited as DSM ACC 2599 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115kD expressed by ASPC-1 (ATCC Accession No. CRL-1682) or expressed by BXPC-3 (ATCC Accession No. CRL-1687) cell". The antecedent portion of the claim is drawn to a purified polypeptide antibody or antigen binding fragment thereof, wherein said polypeptide antibody or antigen binding fragment specifically binds to *an* epitope of a polypeptide having an approximate molecular weight of 115kD expressed by ASPC-1 (ATCC Accession No. CRL-1682) or expressed by BXPC-3 (ATCC Accession No. CRL-1687) cells, which encompasses a broad genus of antibodies binding to a broad genus of epitopes. It is indefinite as to which "said epitope" the PM-2 antibody binds or if the wherein clause limits the claimed antibody or antigen binding fragment to binding the epitope bound by PM-2. Thus, claim 1 and its dependent claims are indefinite. Limiting the claims to an antibody or antigen binding fragment that binds the same epitope as that bound by the PM-2 antibody produced by a cell line deposited as DSM ACC 2600 would obviate this rejection.

Additionally, claim 112 recites the limitation "functional fragment" of the purified antibody of claim 111. There is insufficient antecedent basis for this limitation in claim 111.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 111-116, 120-130 and 134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to the PM-2 antibody produced from a cell line deposited as DSMZ Accession No. DSM ACC25600 and antibodies that bind the epitope bound by the PM-2 antibody produced from a cell line deposited as DSMZ Accession No. DSM ACC2600 producing them.

The specification states that PM-2 cell line was deposited at the German Collection of Microorganisms and Cell Cultures on July 2, 2003 under the terms of the Budapest Treaty (see para bridging p. 21-220, and Applicants have stated in the remarks filed 12/31/2007 that access to the deposited PM-2 cell line will be made in accordance with the provisions of 37 C.F.R. §1.808. Accordingly, as the PM-2 deposit will be made available to the public according to 37 C.F.R. § 1.808 upon issuance of the patent, the grounds for rejection are moot and Applicants respectfully request that withdrawal of the rejection, see page 8 of the remarks filed 12/31/2007

However, Applicant's referral to a cell line deposited as DSMZ Accession No. DSM ACC2600 on July 2, 2003 is insufficient assurance that all of the conditions of 37 CFR 1.801-1.809 have been met in view of Applicant's earlier effective filing date, i.e., 7/4/2002 for the

earliest foreign application priority claimed. If a deposit is made after the effective filing date of the application for patent in the United States, as in the instant application, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b). Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. If Applicants were able to the rejection set forth in section 6 above, claims 111-116 and 120-130 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein said antibody or antigen binding fragment thereof binds to the epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell specifically bound by the PM-2 antibody produced by a cell line deposited as DSM ACC2600, *does not* reasonably provide enablement for a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel

electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell, wherein said antibody binds the carcinomas of claim 126, inhibits proliferation of adenocarcinoma cells of the pancreas in vitro, or inhibits proliferation or induces apoptosis of BXPC-3 cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC

Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell, wherein said antibody binds the carcinomas of claim 126, inhibits proliferation of adenocarcinoma cells of the pancreas in vitro, or inhibits proliferation or induces apoptosis of BXPC-3 cells. Thus, the claims encompass, given the indefinite nature of the "said epitope" in the wherein clause and given their broadest reasonable interpretation, antibodies that bind to a polypeptide or an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells that are distinct from the epitope or polypeptide bound by the PM-2 antibody produced by a cell line deposited as DSM ACC22600. The claims also encompass antibodies or antigen binding fragments comprising sequences with varying identity to SEQ ID NO: 5 and/or 7 that bind this genus of epitopes and proteins. Thus, the claims encompass a genus of antibodies binding to unknown epitopes on unknown proteins.

The specification teaches that SEQ ID NO: 5 and SEQ ID NO: 7 are the amino acid sequences of the variable regions of the light and heavy chains of monoclonal antibody PM-2, see Figure 14 and 15. The specification teaches that the PM-2 monoclonal antibody expressing hybridoma cell line was generated from lymphocytes from pancreatic cancer patients fused to heteromyeloma cell lines. The specification teaches that CDR1 of the PM-2 variable region light chain spans nucleotides 76-102 which encode amino acids 26-34, CDR2 spans nucleotides 154-1

74 which encode amino acids 52-58, and CDR3 spans nucleotides 289-309, which encode amino acids 97- 103. The specification teaches that CDR1 of the PM-2 variable region heavy chain spans nucleotides 3 1-54 which encode amino acids 11-18, CDR2 spans nucleotides 106-129 which encode amino acids 36-43, and CDR3 spans nucleotides 244-300, which encode amino acids 82-100, see Example 2.

The specification teaches that the PM-2 antibody does not stain any normal tissue in immunohistochemical assays, while it positively stains every tumor type tested, see Example 3 and Tables 3 and 4. The specification teaches that The PM-2 antibody specifically binds to the CACO-2 human colorectal adenocarcinoma cell line (ATCC Accession No. HBT-37, DSMZ Accession No. ACC 169), the human colon carcinoma cell line COLO-320 (DSMZ Accession No. ACC 144), the human colon carcinoma cell line COLO-206F (DSMZ Accession No. ACC 2 I), the HT-29 human colorectal adenocarcinoma cell line (ATCC Accession No. HTB-38), ASPC-1 pancreatic carcinoma cells, and BXPC-3 pancreatic carcinoma cell line, see p. 55.

The specification teaches that PM-2 induces apoptosis in BXPC-3 human pancreatic carcinoma cells after 24 hours of incubation, see Example 4, and Fig. 4A and 4B, 7 and 9. Additionally, the specification teaches that PM-2 inhibits the viability and proliferation of human pancreatic carcinoma BXPC-3 cells, see Example 5 and Fig. 3 and 8.

The teachings of the specification cannot be extrapolated to enable the scope of the claims because the claims encompass epitopes and proteins that would not predictably be bound by the PM-2 antibody or antibodies comprising SEQ ID NO: 5 and 7 or variants thereof, i.e. antibodies that bind to a polypeptide or an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis,

wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) that are distinct from the epitope or polypeptide bound by PM-2 because the exquisite sensitivity of binding proteins to alterations of even a single amino acid is well known in the art. For example, Coleman et al. (Research in Immunology, 1994; 145(1): 33-36, previously cited) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Furthermore, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, see abstract in particular) teach single amino acid substitutions outside the antigenic site on a protein affects antibody binding. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Furthermore Pero et al. (US PG Pub 2003/0105000) specifically teach that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50% similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2, see para 0255 of the published application. These references demonstrate that even a single amino acid alteration or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein. Thus, given that the claims encompass PM-2 antibodies and variants thereof to bind to unknown epitopes on unknown proteins and given the unpredictability of the PM-2 antibody interacting with distinct epitopes on

distinct proteins, undue experimentation would be required to make and use the antibody as broadly claimed.

Additionally, one of skill in the art cannot extrapolate the teachings of the specification to the scope of the claim because the claims encompass a genus of antibodies binding a genus of epitopes on a genus of undefined proteins and one of skill in the art cannot predictably expect that this genus of antibodies will induce apoptosis in BXPC3 cells, inhibit proliferation of BXPC3 cells or pancreatic adenocarcinoma cells, or bind to other cancer cell types by targeting the broad genus of epitopes because the ability of an antibody to bind an epitope or antigen is not predictive of other antibody activities towards the cells and the expression a polypeptide by BXPC-3 or ASPC-1 cells is not predictably indicative of the protein's expression by pancreatic adenocarcinoma or other cancers in vivo because of the expression of proteins in cultured cell lines is not predictably indicative of the proteins expression *in vivo* because of the artifacts associated with cultured cells *in vitro* and the heterogeneity of cancer is well known in the art .

As drawn to the correlation between antibody binding to an epitope and other activities of the antibody, Young et al. (US Pat. App. Pub 2004/0258693, Dec. 23, 2004) teach that the monoclonal antibody 7BD-33-11A binds to multiple cell lines, but only induced cytotoxicity in a small subset of those cells to which it bound, see Table 1 and 2 and para. 0100-0102. Additionally, Young et al. (US Patent Application Pub. 2004/0197328, October 7, 2004) teaches that monoclonal antibody 11BD-2E11-2, which is cytotoxic towards some cell lines, binds to MDA-MB-231 cells, but is not cytotoxic towards them, see para 0100-0104 and Tables 2 and 3. Furthermore, Young et al. (US Patent Application Pub. 2004/0197328, October 7, 2004) teach that while monoclonal antibody 11BD-2E11-2, which recognizes Melanoma-associated

chondroitin sulfate proteoglycan (MCSP), is effective for treatment of breast and ovarian tumors (see examples 7 and 8), other monoclonal antibodies that also recognize MCSP, such as 9.2.27 and 225.28S, were generally ineffective as therapeutic antibodies, see para. 0014-0019. Thus even for monoclonal antibodies that recognize the same protein or epitope, it cannot be predicted if the antibody will have the same activity towards different cells expressing the targeted protein or epitope. Furthermore, it is not clear from the teachings of the specification or the art of record if it is the binding of PM-2 to the 115 kDa protein, the 55 kDa protein (see Fig. 5) or an approximately 80 kDa protein with similarity to the integrin binding protein p80 or the protein REV1 (see US Pat. App. Pub. 2008/0281083 (Vollmers et al. Nov. 13, 2008) Abstract and Fig. 3) that is responsible for the activities of the PM-2 antibody in regard to cell proliferation and apoptosis. Thus, given the breadth of the claimed antibodies that bind to a genus of epitopes on a genus of proteins and the unpredictability of correlating the activities of an antibody with its binding to an epitope or protein and given that only the PM-2 antibody that binds the 115 kDa protein expressed by ASPC-1 and BXPC-3 has been shown to induced apoptosis or inhibit proliferation in a single pancreatic cell line, undue experimentation would be required to make an use the invention as broadly claimed.

As drawn to the artifactual nature of cell lines, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor as set forth above. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4, previously cited), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and

their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12: 320, previously cited) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25, previously cited) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802, previously cited) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines

containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Thus, given that claims encompass antibodies that bind unknown epitopes on unknown polypeptides distinct from that bound by PM-2, the expression of these unknown proteins by BXPC-3 or ASPC-3 would not predictably be indicative of the proteins expression in pancreatic carcinoma or other carcinomas *in vivo*.

Additionally, as drawn to cancer heterogeneity, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274, previously cited). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between PM-2 and inhibition of pancreatic cell growth, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850, previously cited), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313: 1370, previously cited) teaches that in a

genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729, previously cited) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between the binding of PM-2 to the two pancreatic cell lines and ASPC-1 and BXPC-3 and the binding of the broadly claimed antibodies, which are not limited to binding the polypeptide bound by PM-2, to the multiple tumor types claimed based on the information in the specification and known in the art without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

In the remarks of May 13, 2009 Applicants argue that, for the reasons of record, Applicants maintain that in view of the guidance in the specification and knowledge and skill in the art concerning antibody structure and function at the time of the invention, and that antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make antibodies and antigen binding fragments that specifically bind to

the recited polypeptide without undue experimentation. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, Applicants have amended claims 121 and 124 and have cancelled claims 145 and 148 without prejudice. Applicants will therefore address the rejection as to amended claims 121 and 124

Amended claim 121 requires all three CDRs of each heavy and light chain variable regions sequence. Accordingly, as all three CDRs are present in the heavy and light chain variable region sequences, the ground for rejection of claim 121 is moot.

Amended claim 124 no longer recites the VL, Vm and Fc, fragments. Accordingly, the ground for rejection of claim 124 is moot.

Applicants argue that in sum, the grounds for rejection are moot in view of the amendments to claims 121 and 124. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement be withdrawn.

Applicants' arguments have been considered, but have been not been found persuasive because the breadth of the claimed antibodies that encompass antibodies that bind unknown epitopes and unknown proteins would require undue experimentation to make and use for the reasons set forth above.

8. Claims 111-116 and 120-130 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide

having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells and wherein PM-2 antibody produced by a cell line deposited as DSM ACC2600 specifically binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cell, wherein said antibody binds the carcinomas of claim 126, inhibits proliferation of adenocarcinoma cells of the pancreas in vitro, or inhibits proliferation or induces apoptosis of BXPC-3 cells. Thus, the claims encompass, given the indefinite nature of the "said epitope" in the wherein clause and given there broadest reasonable interpretation, antibodies that bind to a polypeptide or an epitope of a polypeptide having an approximate molecular weight of 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells that are distinct from the epitope or polypeptide bound by the PM-2 antibody produced by a cell line deposited as DSM ACC22600. The claims also encompass antibodies or antigen binding fragments comprising sequences with varying identity to SEQ ID NO: 5 and/or 7 that bind this genus of epitopes and proteins. Thus, the claims encompass a genus of antibodies binding to unknown epitopes on unknown proteins.

It is well known in the art that there is a lack of a predictable structure function correlation between the structure of antibody or any other binding molecule and binding to an antigen or its epitope within the antigen. In particular Rudikoff et al. (Proc Natl. Acad. Sci. USA 1982 79: 1979-1983, page 1979, previously cited) teach that the alteration of a single

amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. The specification provides no guidance on structure or residues that are critical to the function of broadly claimed antibody or antibody ligand. Although it is clear that binding specificity of the disclosed antibody is determined by the CDR regions, it is well known that this determination requires the exquisite interaction of the CDRs of both the light and heavy chains and the framework region of the antibody. In particular, although drawn specifically to humanization techniques, Gussow et al. (1991, Methods in Enzymology 203:99-121, previously cited) is relevant to the instant rejection. Gussow et al. specifically teaches that the applicability of antibody humanization techniques relies on, among others, the assumption that the frameworks of the variable domains serve as a scaffold to support the CDRs in a specific way that facilitates antigen binding and further teach that it is of great importance to retain the interactions between the donor CDRs and the acceptor framework as closely as possible to the CDR-framework interactions of the original Mab. Gussow et al. further teaches that the affinity of the first fully humanized antibody CAMPATH1 was nearly 40 fold lower compared to the original rat MAb, apparently because of differences of residues in the framework region of the humanized antibody compared to those of the original antibody, particularly those located close to the CDRs. Clearly, alteration of even one amino acid residue can alter the packing of the residues within the molecule as it was demonstrated that mutation of the human Ser 27 to a Phe (the residue found in the original rat antibody at this position) restored the binding affinity of the humanized antibody close to the original affinity (see page 100). Furthermore Pero et al. (US PG Pub 2003/0105000) specifically teach that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but although Grb7 binds to ErbB2, Grb14 does not bind

to ErbB2. Further, although the SH2 domain of Grb2 is only 50% similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2, see para 0255 of the published application. Thus, there is not a predictable structure function correlation between antibody or other binding protein and antigen/epitope binding in the art.

The following teaching of the Federal Circuit as set out in Noelle v. Lederman, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing

mouse CD40CR antigen". Noelle v. Lederman, 69 USPQ2d 1508 (Fed. Cir. 2004) 355 F3d 1343 at 1514.

Thus to satisfy the written description requirement for the broadly claimed genus of antibodies the antigen bound by the antibodies must be adequately described. The Federal Circuit further addresses this issue in *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) 545 F3d 1015, "The specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient. The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language — "a monoclonal antibody idiotypic to the neurofibrosarcoma of said human." This sparse description of antibody structure in the claim stands in stark contrast to the detailed method of *making* the antibodies found in the specification" *In re Alonso*, 88 USPQ2d 1849 (Fed. Cir. 2008) at 1853.

The instant specification has only described the antigen bound by PM-2 by its molecular weight and its expression in cancer cells, thus it fails to describe the genus of antibodies claimed because this does not provide support for the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the broad genus of antibodies claimed. The specification only discloses the PM-2 antibody produced by the hybridoma deposited as DSM ACC 2600. Further, the epitopes are not disclosed for *any* of the disclosed species. Therefore, since the claims encompass a genus of antibodies based on genus of unknown

epitopes on unknown proteins and it is unclear what structures would identify members of the genus.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The instant specification fails to provide sufficient descriptive information, such as definitive structural features that are common to the genus. That is, the specification provides neither a representative number of antibodies that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genus is highly variant, the disclosure of the PM-2 antibody produced by the hybridoma deposited as DSM ACC 2600 is insufficient to describe the genus of broadly claimed antibodies that binds unknown epitopes that are bound by PM-2 or that are not bound by PM-2 on unknown proteins. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the isolated the PM-2 antibody produced by the hybridoma deposited as DSM ACC 2600, antigen binding fragments thereof, a purified antibody or antigen binding fragment comprising the amino acid sequence of SEQ ID NOS: 5 and 7, and a purified polypeptide antibody or antigen binding fragment comprising amino acid 26-34, 52-58, and 97-103 of SEQ ID NO: 5 and amino acids 11-18, 36-43, and 82-100 of SEQ ID NO:7 meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In the remarks of May 13, 2009 Applicants argue that claims 117 to 119, 121,141 to 143 and 145 prior to entry of this paper are adequately described for the reasons of record. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 117 to 119, 141 to 143 and 145 have been cancelled herein without prejudice, and claim 121 has been amended as set forth above. The rejection will therefore be addressed with respect to amended claim 121.

Amended claim 121 requires all three CDRs of each heavy and light chain variable regions sequence. Accordingly, as all three CDRs are present in the heavy and light chain variable region sequences, the ground for rejection of claim 121 is moot.

In sum, the grounds for rejection are moot in view of the amendment to claim 121. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description be withdrawn.

Applicants' arguments have been considered, but have been not been found persuasive because the breadth of the claimed antibodies that encompass antibodies that bind to unknown epitopes and unknown proteins that are not adequately described for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 111 and 124-130 are rejected under 35 U.S.C. 102(b) as being anticipated by Overholser et al. (Cancer 2000 89 (1): 74-82) as evidenced by USPN 6,794,494 (Young et al. April 14, 2003).

It is noted that given the breadth of the claims, the claims are not limited to antibodies that bind the same epitope as that bound by the PM-2 antibody and neither the claims nor the specification the claims limit the range of molecular weights encompassed by an approximate molecular weight of 115 kDa.

Overholser et al. teach that the monoclonal antibody IMC-C225 binds an epitope of a polypeptide, the epidermal growth factor receptor (EGFR), expressed by BXPC-3 cells and inhibits proliferation and induces apoptosis in these pancreatic adenocarcinoma cells, see Abstract, Fig. 1-3, Tables 1 and 2, and p. 78-pargraph bridging the two columns. Overholser et al. teach using the IMC2-225 antibody in western blots in which the antibody is linked to a detectable agent, see Fig. 1.

USPN 6,794,494 teaches that the c225 antibody binds EGFR in CACO-2 cells, see Table 3.

10. Claims 111-116, 120-130, and 134 are rejected

11. Claims 133 appears allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642